AWARD NUMBER:  W81XWH-15-2-0049


TITLE: Automated Comprehensive Evaluation of mTBI Visual Dysfunction


PRINCIPAL INVESTIGATOR: LTC Jose E. Capo-Aponte


CONTRACTING ORGANIZATION:  Geneva Foundation
Tacoma, WA 98402


REPORT DATE: October 2016


TYPE OF REPORT:  Annual


PREPARED FOR:   U.S. Army Medical Research and Materiel Command
                Fort Detrick, Maryland  21702-5012


DISTRIBUTION STATEMENT: Approved for Public Release;
                        Distribution Unlimited

# REPORT DOCUMENTATION PAGE

*Form Approved*
*OMB No. 0704-0188*

| 1. REPORT DATE | 2. REPORT TYPE | 3. DATES COVERED |
|---|---|---|
| October 2016 | Annual | 15 Sep 2015 - 14 Sep 2016 |

**4. TITLE AND SUBTITLE**
Automated Comprehensive Evaluation of mTBI Visual Dysfunction

**5a. CONTRACT NUMBER**
W81XWH-15-2-0049

**5b. GRANT NUMBER**

**5c. PROGRAM ELEMENT NUMBER**

**6. AUTHOR(S)**
LTC Jose E. Capo-Aponte

E-Mail: Jose.E.CapoAponte.mil@mail.mil

**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

Geneva Foundation
Tacoma, WA 98402

Womack Army Medical Center
2817 Reilly Rd; Stop A
Fort Bragg, NC 28310-7301

**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

**10. SPONSOR/MONITOR'S ACRONYM(S)**

**11. SPONSOR/MONITOR'S REPORT NUMBER(S)**

**12. DISTRIBUTION / AVAILABILITY STATEMENT**

Approved for Public Release; Distribution Unlimited

**13. SUPPLEMENTARY NOTES**
mild traumatic brain injury, mTBI, objective biomarkers, Neuro-Ophthalmic Device, NODe

**14. ABSTRACT**

The purpose of this study is to validate the Neuro-Ophthalmic Device (NODe) test battery that provides the highest sensitivity and specificity for the detection of oculomotor and high order visual processing dysfunctions on a large population of Warfighters with acute mTBI as compared to healthy age-matched controls. This study also will demonstrate that a comprehensive combination of biomarkers will be more specific to mTBI than any one test alone and that the tests within the NODe test battery can serve as objective biomarkers for acute mTBI. Two hundred acute mTBI (≤72 hrs post injury) and 200 age-matched non-TBI (controls) military personnel will be recruited from the patient population at Womack Army Medical Center (WAMC). The central hypothesis is that a NODe test panel evaluating visual function can detect neurological and ophthalmological changes induced by acute mTBI compared to age-matched controls.

**15. SUBJECT TERMS**

Nothing listed

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON USAMRMC |
|---|---|---|---|---|---|
| **a. REPORT** | **b. ABSTRACT** | **c. THIS PAGE** | Unclassified | 10 | **19b. TELEPHONE NUMBER** (include area code) |
| Unclassified | Unclassified | Unclassified | | | |

**Standard Form 298 (Rev. 8-98)**
Prescribed by ANSI Std. Z39.18

# Table of Contents

**INTRODUCTION**:

The DOD reported that 333,169 cases of traumatic brain injury (TBI) were confirmed since 2000, with mild TBI (mTBI) accounting for 82.4%. The diagnosis of mTBI has been a challenge for the military primarily because of the lack of objective assessment tools, overlap of symptoms in co-morbid conditions such as post-traumatic stress disorder (PTSD), and the interpretation of signs and symptoms by healthcare providers relies on self-reported symptoms from the injured Warfighters. Somatosensory disruptions following mTBI can include impairments of vision, equilibrium, smell, hearing, taste, and somatosensory perception. These sensory disruptions are frequently caused by trauma to the sensory organs or their projections through the brain stem to central processing systems. Several studies have identified oculomotor dysfunctions (OMDs) (i.e., version, vergence, and accommodation) to be the most common visual deficits associated with mTBI. Because of the prevalence of vision-related problems after TBI and their consequences for functional performance, experts recommend screening for vision deficits early in patients' recovery. However, the absence of standardized methodology to complete ocular and vision testing among military eye-care providers (e.g., primary care, occupational therapists, optometrists and ophthalmologists) may lead to no diagnosis or misdiagnosis of post-mTBI-related vision problems. The purpose of this study is to validate the Neuro-Ophthalmic Device (NODe) test battery that provides the highest sensitivity and specificity for the detection of oculomotor and high order visual processing dysfunctions on a large population of Warfighters with acute mTBI as compared to healthy age-matched controls. This study also will demonstrate that a comprehensive combination of biomarkers will be more specific to mTBI than any one test alone and that the tests within the NODe test battery can serve as objective biomarkers for acute mTBI. Two hundred acute mTBI (≤72 hrs post injury) and 200 age-matched non-TBI (controls) military personnel will be recruited from the patient population at Womack Army Medical Center (WAMC). The central hypothesis is that a NODe test panel evaluating visual function can detect neurological and ophthalmological changes induced by acute mTBI compared to age-matched controls.

**KEYWORDS:**

mild traumatic brain injury, mTBI, objective biomarkers, Neuro-Ophthalmic Device, NODe

**ACCOMPLISHMENTS**:

- **What were the major goals of the project? / What was accomplished under these goals?**

**Specific Aim 1: Clinical Study Data Collection - Collect NODe data for n = 200 controls and n = 200 personnel with a diagnosis of mTBI during the acute phase (< 72 hrs) of presentation.**

**Major Task 1: IRB/HRPO approval and hiring/identification of required study personnel.**
Subtask 1: Obtain IRB/HRPO approval for the proposed study. **COMPLETED**
There was significant delay in getting protocol processed and approved. While the original protocol was submitted to the WAMC IRB on 16 Sep 2015, the WAMC Institutional Review Board (IRB) experienced significant processing delays caused by Defense Health Agency (DHA) inactivation of IRBNet on 29 Sep 2015. The study protocol received initial approval from WAMC IRB on 28 Dec 2015 with an Addendum correction dated 8 Jan 2016. The protocol also received initial USAMRMC HRPO approval on 3 Mar 2016. After initial approvals were received, significant changes were needed to accommodate the requirements by the Federal Interagency Traumatic Brain Injury Research (FITBIR) reporting regarding the collection of personally identifiable information (PII)

required to create the unique identifier for subjects. The final approval by USAMRMC HRPO was received on 17 May 2016. The WAMC IRB approved study annual Continuing Review on 24 Oct 2016.

Subtask 2: Hire personnel required at WAMC and study personnel training: **COMPLETED**
The Ophthalmic Assistant (also serving as Study Coordinator) was hired on 1 Oct 2015. In mid-November 2015, the research Optometrist required for the study was conditionally hired by the Geneva Foundation and initiated in-processing at WAMC. However, due to significant delays in getting the government background check processed, the employee opted to find another employment. The Geneva Foundation restarted recruiting efforts and a full-time research Optometrist was hired on 4 Apr 2016.

Subtask 3: Data management and IM/IT consultant (TBD) to draft a NODe DoD IM/IT strategic roadmap, implement NINDS CDE data compatibility and FITBIR sharing processes: **COMPLETED**
Two NODEs units were delivered and calibrated by the Brien Holden Vision Diagnostics (BHVD) collaborator and all research team members were training in data collection procedures. An excel database was created to enter collected data. The Federal Interagency Traumatic Brain Injury Research (FITBIR) account was created and the Principal and Associate investigator completed FITBIR training. Currently, data is being reported to the FITBIR.

**Major Task 2: Data collection (n = 400 subjects).**
Subtask 1: Subject recruitment through DBIM and Department of Optometry: **IN PROGRESS**
A total of 66 subjects were recruited for the study, but only 62 meet the inclusion criteria.

Subtask 2: Data collection with the NODe and other evaluation tools: **IN PROGRESS**
Complete data sets were collected for 62 subjects (17 mTBI and 45 Controls).

Subtask 3: Data archiving and storage, batch data analysis and mining for results: **IN PROGRESS**
Data collected for the 62 subjects have been entered in the appropriate excel format to facilitate reporting to FITBIR and future data analysis.

**Specific Aim 2: Data analysis for Sensitivity and Specificity of the NODe mTBI Test Panel.**

**Major Task 1: Evaluate sensitivity and specificity of the NODe.**
Subtask 1: Statistical analysis of NODe data from controls and mTBI patients: **NOT INITIATED**
No sufficient data has been collected for each group at this point to have sufficient sample size power for a preliminary data analysis.

Subtask 2: Define the clinical mTBI diagnosis as the gold standard and evaluate NODe metrics for sensitivity and specificity to diagnosed mTBI. Evaluate the likelihood of developing a bimodal threshold for mTBI screening assuming one or more clustered NODe metrics from the metrics in Table 7 of the Project Narrative: **NOT INITIATED**
A complete data set is required to accomplish this subtask.

**Major Task 2: Evaluate sensitivity and specificity of the NODe Establish relationship with existing clinical tools.**
Subtask 1: Measure NODe's clinical performance. Measure how well NODe's test results correlate with the clinical diagnosis in the intended use populations. Specifically, how well clinical report results (e.g., clinical data and ANAM) of the mTBI diagnosis correlate with NODe's test results:

**NOT INITIATED**
A complete data set is required to accomplish this subtask.

Subtask 2: Provide recommendations for integration of the NODe into the existing mTBI screening and injury recovery paradigm. Manuscript generation: **NOT INITIATED**
A complete data set is required to accomplish this subtask.

**Specific Aim 3: NODe Data Sharing and DoD Strategic Roadmap Development. The data collected from the NODe system will be shared as per the Data Management and Data and Research Resources Sharing Plan documents. NODe data will not integrated with information systems at WAMC or other locations within the DoD in the proposed study. However, a roadmap for future required steps and insertion points for collected NODe data into outpatient (e.g., Armed Forces Health Longitudinal Technology Application [AHLTA]) and operational (e.g., Joint Trauma System) and other TBI-relevant databases (e.g., Federal Interagency Traumatic Brain Injury Research [FITBIR]) will be reported.**

**Major Task 1: Customized DoD-focused report generation.**
Subtask 1: NODe results are translated into an operator-defined set of reports based on the NODe battery metrics that are most indicative of mTBI. The NODe reports will support provider decision-making in clinical and operational settings, as well as serving as a useful adjunct for guiding additional functional assessments or additional screening (e.g., advanced neuroimaging).
**NOT INITIATED**
A complete data set is required to accomplish this subtask.

**Major Task 2: Data research and resource sharing plan.**
Subtask 1: Data collected will be compatible with the National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements (CDE). Provide quarterly datasets into FITBIR.
**IN PROGRESS**
Study data is uploaded into FITBIR on quarterly basis.

**Major Task 3: NODe DoD transition plan and DoD strategic roadmap development.**
Subtask 1: Delineate a phased innovation plan to move the NODe and future iterations of this technology to forward echelons of operational healthcare. **NOT INITIATED**
A complete data set is required to accomplish this subtask.

Subtask 2: Develop DoD-focused documentation for operator-specific training purposes.
**NOT INITIATED**
A complete data set is required to accomplish this subtask.

Subtask 3: Develop a DoD Strategic Roadmap for insertion of NODe data into AHLTA and other systems (Joint Trauma System). Evaluate the required technology translation capabilities (intended use in DoD locations, IM/IT insertion points, NODe operationalization, and telemedicine support) to create a roadmap of next steps within the final study report. IM/IT consultant (TBD) will provide guidance. **NOT INITIATED**
A complete data set is required to accomplish this subtask.

- **What opportunities for training and professional development has the project provided?**
Nothing to Report

- **How were the results disseminated to communities of interest?**

Nothing to Report

- **What do you plan to do during the next reporting period to accomplish the goals?**

Study team will continue recruitment and data collection.

- **What was the impact on the development of the principal discipline(s) of the project?**

Nothing to Report

- **What was the impact on other disciplines?**

Nothing to Report

- **What was the impact on technology transfer?**

Nothing to Report

- **What was the impact on society beyond science and technology?**

Nothing to Report

**IMPACT**

Nothing to Report.

**CHANGES/PROBLEMS**

Nothing to Report

**PRODUCTS**
- **Journal publications.**

Nothing to Report.

- **Books or other non-periodical, one-time publications.**

Nothing to Report

- **Other publications, conference papers, and presentations.**

Nothing to Report

- **Website(s) or other Internet site(s)**

Nothing to Report

- **Technologies or techniques.**

Nothing to Report

- **Inventions, patent applications, and/or licenses.**

Nothing to Report

- **What was the impact on technology transfer?**

Nothing to Report

- **Other Products?**

Nothing to Report

**PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**
- **What individuals have worked on the project?**

| | |
|---|---|
| Name: | LTC Jose E. Capo-Aponte, OD, PhD |
| Project Role: | Principal Investigator (PI); Research Optometrist |
| Nearest person month worked: | 12 |
| Contribution to Project: | Provided overall study oversight, protocol development and amendments, ensuring adherence to the protocol, reporting any deviations from protocol, and reports preparation. |
| Funding Support: | Womack Army Medical Center |

| | |
|---|---|
| Name: | Wesley R. Cole, Ph.D |
| Project Role: | Associate Investigator; Neuropsychologist |
| Nearest person month worked: | 1 |
| Contribution to Project: | Assisted with study oversight, protocol and amendments development, ensuring adherence to the protocol, reporting any deviations from protocol, recruiting, informed consent, and reports preparation. |
| Funding Support: | Defense and Veterans Brain Injury Center (DVBIC) |

| | |
|---|---|
| Name: | Barbara A. Wujciak, OD, MPH |
| Project Role: | Research Optometrist |
| Nearest person month worked: | 7 |
| Contribution to Project: | Assisted with amendments development, ensuring adherence to the protocol, recruiting, informed consent, data collection. |
| Funding Support: | Award |

| | |
|---|---|
| Name: | Jacques Arrieux, M.A. |
| Project Role: | Research Assistant |
| Nearest person month worked: | 2 |
| Contribution to Project: | Assisted with recruiting, consenting and data collection. |
| Funding Support: | Defense and Veterans Brain Injury Center (DVBIC) |

| | |
|---|---|
| Name: | Brad Bower, PhD |
| Project Role: | Research Assistant |
| Nearest person month worked: | 6 |

| | |
|---|---|
| Name: | Joseph Dumayas, M.S |
| Project Role: | Ophthalmic Assistant; Study Coordinator |
| Nearest person month worked: | 12 |
| Contribution to Project: | Coordinated research activities between team members of the Optometry Department and the Department of Brain Injury Medicine. In addition, conducted recruiting, consenting and data collection. |
| Funding Support: | Award |

Contribution to Project:                    Installed the NODe devices, trained research team in NODe administration, assisted with report preparation as well as FITBIR data entry and reporting

Funding Support:                           Brien Holden Vision Diagnostics (BHVD)

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to Report

- **What other organizations were involved as partners?**

**Organization Name:** Defense and Veterans Brain Injury Center (DVBIC)
**Partner's contribution to the project:** Personnel exchanges and collaboration.

**Organization Name:** Brien Holden Vision Diagnostics (BHVD)
**Partner's contribution to the project:** Personnel exchange and collaboration. Also provided two NODe devices in-kind and associated training.

**SPECIAL REPORTING REQUIREMENT**

**APPENDICES**:
Nothing to Report

# Automated Comprehensive Evaluation of mTBI Visual Dysfunction

**MR141268 FY14 CDMRP DMRDP CRMRP-JPC8 PH-TBI NSRRA**
**W81XWH-15-2-0049**

**PI:** LTC Jose Capo-Aponte OD, PhD  **Org:** The Geneva Foundation / Womack AMC / Brien Holden Vision Diagnostics     **Award Amount:** $858,048

## Study/Product Aim(s)

• Objective: Utilize a panel of Neuro-Ophthalmic Device (NODe) tests to assist with screening/diagnosis of visual dysfunctions induced by mild traumatic brain injury (mTBI). Potential use as objective mTBI biomarker
• Hypothesis: Combination of binocular, oculomotor, higher-order visual processing will be more specific to mTBI than one test alone
•  Validate sensitivity/specificity in large population with acute mTBI.
• Translate custom NODe mTBI panel and advanced analytics for clinic use; identify IM/IT data integration points and NODe optimization for forward echelon utilization/telemedicine.

## Approach

This is a prospective study to define and validate the NODe test battery that provides the highest sensitivity and specificity for the detection of oculomotor and high order visual processing dysfunctions on a large population of Warfighters with acute (≤72 hrs) mTBI (n=200) as compared to healthy age-matched controls (n=200).



Neuro-Ophthalmic Device (NODe)

Accomplishment: Received all administrative approvals and completed data collection on 62 subjects.

## Timeline and Cost

| Activities                                                                 FY | 16 | 17 |
|-------------------------------------------------------------------------------|------|------|
| IRB/HRPO Approval & hiring of required study personnel                        | ▮ | |
| Data collection (200 mTBI + 200 controls) & data entry for analysis; FITBIR reporting | ▮ | |
| Data analysis to determine NODe Sensitivity and Specificity; Reports & Manuscripts | | ▮ |
| NODe DoD strategic roadmap (transition plan for operational demo, IM/IT, telemedicine) | | ▮ |
| **Estimated Budget ($K)** | **$420** | **$438** |

**Updated:** 10/26/2016

## Milestones

**FY16-17 Goals** – NODe data collection and analyses
☑ Receive regulatory approvals and Hiring study personnel
☐ NODe data collection for n=200 mTBI cases and n=200 controls
☐ Sensitivity/specificity and clinical performance analyses from NODe, clinical, and neuropsychological data
☐ Reports and manuscript development
**FY17 Goals** – NODe data sharing & DoD Strategic Roadmap Developed
☐ Data sharing; IM/IT insertion point requirements to current systems as required (e.g., AHLTA, JTS) Operational requirements including clinical integration plan, training documents, and telemedicine roadmap

## Comments/Challenges/Issues/Concerns

•  Initially, experienced delays getting protocol approval and recruiting staff. Currently have all approvals and staffing in place; therefore, expected to continue to enrolled subjects without any issues.

## Budget Expenditure to Date

Projected Expenditure: $429,024
Actual Expenditure:  $283,679.06